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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/817,507	04/17/1997	TADAMITSU KISHIMOTO	53466/201	8301

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EXAMINER

CANELLA, KAREN A

ART UNIT PAPER NUMBER

1643

DATE MAILED: 04/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

08/817,507

Applicant(s)

KISHIMOTO ET AL.

Examiner

Karen A. Canella

Art Unit

1643

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 15 and 24-28 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☐ Claim(s) 15 and 24-28 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. ____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|--|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date ____ | 6) <input type="checkbox"/> Other: ____ |

DETAILED ACTION

Claims 15 and 24-28 are pending and under consideration.

Sections of Title 35 U.S. Code not found in this action can be found in a previous action.

The rejection of claims 15 and 24-28 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained for the reasons of record below. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

(A)As drawn to the treatment of elevated blood levels of ionized calcium

Claim 15 is drawn to a method of treating a patient suffering from an elevated blood level of ionized calcium accompanied by cachexia caused by Il-6 production, said method comprising administering to said patient a therapeutically effective amount of an antibody to an Il-6 receptor in a pharmaceutically acceptable carrier to suppress elevation of blood level of ionized calcium and wherein the therapeutically effective amount blocks signal transduction by Il-6 and inhibits the binding of Il-6 to the Il-6 receptor.

The specific limitation of “elevated blood level of ionized calcium” was added in an amendment filed August 28, 2001. The specification as filed states on page 2, lines 6-9, that the present invention provides pharmaceutical compositions for the treatment of diseases caused by Il-6 production. On page 3, lines 26-30, the specification states that diseases caused by Il-6 production include plasmacytosis such as rheumatism and Castleman’s disease, hyperglobulinemia, anemia, nephritis, cachexia etc. It is noted that no specific mention is made of hypercalcemia as a disease caused by Il-6 production. The specification states (pages 25, line 36 to page 26, line 3, and page 26, line 35 to page 27, last line) that the level of ionized calcium was strongly suppressed in cachexic mice treated with the MR16-1 antibody relative to the non-treated group. This specification does not provide adequate written description for the amendment which requires the treatment of a patient suffering from elevated blood levels of ionized calcium associated with cachexia rather than the treatment of cachexia. One of skill in the art upon reading the specification as filed would not have concluded that the method of

Art Unit: 1643

treatment was confined to those individuals suffering from cachexia induced hyperglycemia as the specification clearly states the intention of treating cachexia. Further it is recognized in the art that hypercalcemia associated with malignancy is observed in patients who are a few months from death (Potts, J. T. , In: Harrison's Principles of Internal Medicine, 12 Ed., Wilson et al, Ed, 1991, page 1902). Thus, limitation of the treatment to only a subset of patients with cachexia is not supported by the specification or claims as filed, because it restricts the treatment of patients suffering from cachexia to those exhibiting high levels of blood calcium, and said restriction is not supported by the specification or claims as filed.

applicant argues that the specification supports the phrase "elevated blood levels of ionized calcium" and elevated blood levels of ionized calcium accompanied by cachexia". Applicant cites Example 3 for the induced cachexic model accompanied by hypercalcemia. All of applicants arguments have been considered but not found persuasive. Although the specification sets forth a mouse model of cachexia accompanied by hypercalcemia, there is no contemplation in the specification of the exclusive treatment of cachexia only when accompanied by hypercalcemia. although the specification teaches that levels of ionized calcium decreased in the blood of cachexic mice undergoing treatment with the PM-1 antibody, this does not provide support for limiting the treatment of individuals having cachexia and hypercalcemia rather than individuals having cachexia without hypercalcemia.

Applicant argues that the term "cachexia induced hyperglycemia" is not relevant to the examiners argument. This was a simple word processing error which substituted hyperglycemia for hypercalcemia. Applicant argues that the teachings of Harrison does not undermine what is taught in the specification. However, applicant is ignoring what was taught by Harrison, specifically that not all patients having cachexia also have hypercalcemia. Thus, because the specification clearly states that intention to treat cachexia, without specific support in the specification, the narrowing of the claims to only treat those cachexia patients having hypercalcemia is new matter. Applicant argues that the description need not be in *ipsis verbis*. However, there is no alternative language in the specification for the narrowing of the cachexia population which would be treated by the instant method claims.

Art Unit: 1643

The rejection of claim 15 under 35 U.S.C. 103(a) as being unpatentable over Yoneda et al (Cancer Research, 1993, vol. 53, pp. 737-740) in view of Shimamura et al (U.S. 5,639,455) is maintained for reasons of record.

Yoneda et al teach that administration of anti-IL6 antibodies to mice carrying tumors associated with increased production of Il-6 lowered the blood calcium level in said mice (page 738, first column, line 11 under the heading "Results" to column 2, line 2). Yoneda et al did not teach the administration of anti-IL6-receptor antibodies.

Shimamura et al teaches that antibodies to Il-6 or antibodies to the Il-6 receptor can inhibit the binding of Il-6 to the Il-6 receptor. Shimamura et al teach the administration of a peptide which inhibits the binding of Il-6 to the Il-6 receptor for the treatment of cancer cachexia (column 9, lines 10-11). Thus, Shimamura et al teaches the treatment of cachexia by the blocking of Il-6 binding to the Il-6 receptor, and teaches that antibodies to the Il-6 receptor can serve to block the binding to Il-6 to the Il-6 receptor.

It would have been prima facie obvious at the time the claimed invention was made to treat hypercalcemia associated with cachexia by administering an anti-Il-6 receptor antibody that blocks the binding of Il-6 to the Il-6 receptor. One of skill in the art would have been motivated to do so by the teachings of Yoneda et al who demonstrate that antibodies which neutralize Il-6 cause a decrease in blood calcium levels in mice suffering from cachexia, and the teachings of Shimamura et al on the treatment of cachexia by peptides which block the binding of Il-6 to the Il-6 receptor and the further teachings of Shimamura et al that anti-Il-6 receptor antibodies can also block the binding of Il-6 to the Il-6 receptor. Thus, one of skill in the art would conclude that the blocking of Il-6 from binding to the Il-6 receptor which was demonstrated by Yoneda et al to lower blood calcium levels could also be carried out by the blocking of Il-6 from the Il-6 receptor using an anti-Il-6 receptor antibody.

The rejection of claims 15, 24 and 25 under 35 U.S.C. 103(a) as being unpatentable over Yoneda et al and Shimamura et al as applied to claim 15 above, and further in view of Schwabe et al (Journal of Biological Chemistry, 1994, Vol. 10, pp. 7201-7209) is maintained for reasons of record..

Art Unit: 1643

The combination of Yoneda et al (Cancer Research, 1993, vol. 53, pp. 737-740) in view of Shimamura et al (U.S. 5,639,455) render obvious claims 15 and 24 for the reasons set forth above. Neither reference teaches the PM-1 antibody.

Schwabe et al teach that the anti-Il6 receptor antibody, PM-1, completely inhibited the binding of Il-6 to the Il-6 receptor (page 7204, lines 27-29).

It would have been prima facie obvious at the time the invention was made to use the PM-1 antibody for the treatment of hypercalcemia associated with cachexia. One of skill in the art would have been motivated to do so by the teachings of Schwabe et al on the ability of the PM-1 antibody to block the formation of the Il-6-Il-6 receptor complex.

The rejection of claims 15 and 24-28 under 35 U.S.C. 103(a) as being unpatentable over Yoneda et al and Shimamura et al and Schwabe as applied to claims 15, 24 and 25 above, and further in view of Tsuchiya et al (5,795,965) is maintained for reasons of record.

The combination of Yoneda et al and Shimamura et al and Schwabe render obvious the limitations of claims 15, 24 and 25 for the reasons set forth above. The combination does not teach a chimeric or humanized antibody.

Tsuchiya et al teaches the chimeric and reshaped human PM-1 antibody for therapeutic purposes (column 7, lines 21-37, column 46, lines 59-67 and claim 6). Tsuchiya et al teaches that mouse antibodies are highly immunogenic in humans and therefore cannot be administered in multiple doses without generating an immune response which interferes with the planned efficacy of the administered antibody (column 1, lines 52-59). Tsuchiya et al teaches a reduction in immunogenicity by using chimeric (column 1, line 60 to column 2, line 9) and humanized (column 2, lines 10-22).

It would have been prima facie obvious at the time the invention was made to use the chimeric or reshaped humanized antibody to PM-1 in the invention rendered obvious by the combination of Yoneda et al and Shimamura et al and Schwabe. One of skill in the art would have been motivated to do so by the teachings of Tsuchiya et al on the decrease in immunogenicity afforded by both the chimeric and humanized antibodies.

Art Unit: 1643

Applicant argues that although the examiner “suggests” that Yoneda et al teaches the administration of anti-Il-6 antibodies lowered blood calcium levels associated with increased production of Il-6, the references does not provide for the administration of anti-Il-6 receptor antibodies. Firstly, the fact of the matter is Yoneda et al does indeed teach the administration of anti-Il-6 antibodies as evidenced by the title of the paper. It is noted that this is objectively demonstrated by Yoneda et al and does not require a “suggestion” by the examiner. Secondly applicant argues that the Yoneda reference does not suggest that hypercalcemia is associated with cachexia, or that the administration of anti-Il-6 antibodies suppressed the “elevated blood levels of ionized calcium accompanied by cachexia”. this has been considered but not found to be persuasive. Yoneda et al states on page 738, second column, lines 3-5 that “MH-85 tumor-bearing mice manifested leukocytosis and cachexia (decrease in body weight) as well as hypercalcemia”. Yoneda et al states on page 738, first column, lines 15-17, “When MN-85 tumor bearing nude mice received repeated s.c. injections of the antibodies to human Il-6, there was a progressive decrease in Ca^{2++} ”. It is noted that the MN-85 implanted tumor is a human tumor secreting human Il-6. Applicant argues that while the reference teaches that the anti-Il-6 antibodies may reverse the hypercalcemia, the reference does not teach that the anti-Il-6 antibodies reverse hypercalcemia accompanied by cachexia and cites page 738, second column, lines 6-8. This has been considered but not found persuasive. The instant claims are drawn to the treatment of a patient suffering from elevated blood levels of ionized calcium accompanied by cachexia. Firstly, when given the broadest reasonable interpretation, the term “treatment” encompasses inhibiting the progress of the hypercalcemia associated with cachexia as well as the reversal of the hypercalcemia. thus, it is not required that the combination of references render obvious the “reversal” of the condition. If one of skill in the art would have a reasonable expectation of the success of inhibiting the progress of the hypercalcemia associated with cachexia it would render the claim obvious. thus applicants arguments regarding the “reversal” of the hypercalcemia are moot. further, applicant differentiates between malignancy associated hypercalcemia and hypercalcemia accompanied by cachexia and states that the references does not suggest that the anti-Il-6 antibodies could reverse the hypercalcemia associated with cachexia. this has been considered but not found persuasive. As stated above, the reference teaches that the MN-85 mice which were treated with the anti-Il-6 antibodies exhibited

Art Unit: 1643

leukocytosis, cachexia and hypercalcemia. Thus, applicants argument is moot. Applicant argues that the reference teaches away from the instant invention because Yoneda et al states that the anti-Il-6 antibodies did not produce a statistically significant alteration in the further progress of the cachexia. As stated above, it is not required to inhibit the progress of the cachexia, as decreasing the level of ionized blood calcium levels would fulfill the method objective of "treatment" and the claim limitation of "therapeutically effective".

Applicant again argues that nothing in Yoneda et al teaches that elevated calcium and cachexia are linked. This is again unpersuasive for the reasons set forth above, namely that Yoneda et al teach that the MN-85 mice which were treated with the anti-Il-6 antibodies exhibited leukocytosis, cachexia and hypercalcemia and that administration of the anti-Il-6 antibodies caused a decrease in the level of ionized calcium.

Applicant argues that Yoneda et al do not teach the use of an Il-6 receptor antibody. It is noted that Shimamura et al is relied upon for this teaching, so the lack of teaching in Yoneda et al is not relevant to the instant obviousness rejection. Applicant argues that because an anti-Il-6 antibody could be demonstrated to block a particular phenomenon, does not necessarily indicate that an anti-Il-6 receptor antibody would block the same phenomenon. This has been considered but not found persuasive. Yoneda et al specifically used "neutralizing antibodies to Il-6". Thus, one of skill in the art can reasonably conclude that binding to the neutralizing antibody would prohibit Il-6 from binding to the Il-6 receptor and thus the activity of the Il-6 cytokine is "neutralized". Shimamura et al teach that antibodies to the Il-6 receptor can inhibit the binding of Il-6 to the il-6 receptor and demonstrates the blocking of the Il-6 receptor using peptides which bind thereto and inhibit the binding of Il-6 in order to avoid immunogenicity. Shimamura et al teaches that there is a strong correlation between Il-6 and cancer cachexia (column 1, lines 62-65). Shimamura et al teach that methods which suppress the activity of human Il-6 include inhibition of the binding of Il-6 produced to receptors and that the methods of inhibiting the binding of Il-6 to receptors are capable of selectively suppressing only the function of Il-6 and thus have the least side-effects (column 3, lines 10-19). Shimamura et al teach that agents which inhibit the binding of human Il-6 to human Il-6 receptors include mouse anti-Il-6 antibody and mouse anti-Il-6 receptor antibody (column 3, lines 20-23). Shimamura et al teaches an alternative agents which are peptides which inhibit the binding of Il-6 to the Il-6 receptor in order

Art Unit: 1643

to avoid the HAMA response (column 3, lines 23-31 and column 5, lines 4-15). Applicant argues that because the blood contained soluble Il-6 receptors in addition to Il-6, a skilled artisan could understand that anti-Il-6 antibodies would also bind to soluble Il-6 receptors. Applicant argues that because the blood contained a larger amount of Il-6 receptor compared to that of Il-6, one of skill in the art would not necessarily expect to observe the same result as with the administration of the Il-6 antibody. This has been considered but not found persuasive. One of skill in the art would understand that while some of the anti-Il-6 receptor antibody was taken up by soluble receptor, it would be necessary to increase the dosage of said antibody. Applicant further argues that one of skill in the art would conclude that the Il-6-anti-Il-6 complex would be neutralized due to elimination of the antibody complex through the scavenging receptors in the reticulo-endothelial system, but due to the fact that the Il-6 receptor is located on a cell surface, scavenging would not occur. This has been considered but not found persuasive. Scavenging of the antibody-Il-6 complex is only one means for decreasing the activity of Il-6, another is sterically hindering the binding of Il-6 to the Il-6 receptor, as is exemplified by the peptides which bind to Il-6 used by Shimamura et al to block the binding of Il-6 to the Il-6 receptor. Said peptides are selected from the antigen-binding portions of antibodies which bind to Il-6 (column 6, lines 3-9 and column 13, example 5). Thus, the peptides of Shimamura et al would be devoid of the Fc immunoglobulin portion and could not neutralize Il-6 by scavenger receptors. One of skill in the art would conclude that binding of the peptides to Il-6 physically blocks the binding of Il-6 to the Il-6 receptor which is what is taught by Shimamura et al (column 3, lines 12-14). One of skill in the art would conclude that the anti-Il-6 receptor antibodies taught by Shimamura et al to be effective at blocking the binding of Il-6 to the Il-6 receptor would also function as a physical blocking of the interaction of Il-6 with the Il-6 receptor.

Applicant concludes that Shimamura et al either alone or in combination with Yoneda et al does not teach that anti-

Il-6 receptor antibodies could be used to treat/suppress elevated blood levels of ionized calcium, or that cachexia was associated with elevation of calcium blood levels. It is again noted that the MN-85 mice of Yoneda et al exhibited leukocytosis, cachexia and hypercalcemia and that administration of the anti-Il-6 antibodies caused a decrease in the level of ionized calcium. Thus, elevated levels of Il-6 are associated with hypercalcemia associated with cachexia and the

Art Unit: 1643

blocking of the action of Il-6 caused a decrease in the blood calcium levels, and the teachings of Shimamura et al indicate that the action of Il-6 can be blocked with an anti-Il-6 receptor antibody.

Applicant argues that Schwabe et al teaches nothing about cachexia or elevated calcium levels in the blood. This has been considered but not found persuasive. Schwabe et al is not relied upon for such teachings. Schwabe is relied upon solely for the specific anti-Il-6 receptor antibody required by the claims.

Applicant argues that the reference of Tsuchiya et al cannot cure the deficiency of the teachings of Yoneda et al, Shimamura et al or Schwabe et al because said reference only teaches chimeric or reshaped PM-1 for human purposes. This was considered but not found persuasive. Again, Tsuchiya et al was not relied upon for teachings regarding cachexia or hypercalcemia. Tsuchiya et al was relied upon solely for the chimeric or reshaped PM-1 antibody.

All other rejections or objections are withdrawn in light of applicant's arguments.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 11 am to 10 pm, except Wed, Fri.

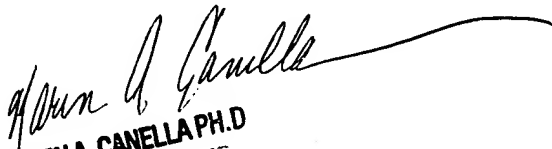
Art Unit: 1643

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.

4/12/2006


KARENA CANELLA PH.D
PRIMARY FY 08/08/06